PD5486

PROLEUKIN®
Aldesleukin
For Injection

WARNING

PROLEUKIN® (aldesleukin for injection) should be administered only in a hospital setting under the supervision of a qualified physician experienced in the use of anti-cancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.

Proleukin administration has been associated with capillary leak syndrome (CLS). CLS results in hypotension and reduced organ perfusion which may be severe and can result in death.

Therapy with Proleukin should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with normal thallium stress tests and pulmonary function tests who have a history of prior cardiac or pulmonary disease.

Proleukin administration should be held in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

DESCRIPTION

PROLEUKIN® (aldesleukin), a human recombinant interleukin-2 product, is a highly purified protein with a molecular weight of approximately 15,300 daltons. The chemical name is des-alanyl-1, serine-125 human interleukin-2. Proleukin, a lymphokine, is produced by recombinant DNA technology using a genetically engineered *E. coli* strain containing an analog of the human interleukin-2 gene. Genetic engineering techniques were used to modify the human IL-2 gene, and the resulting expression clone encodes a modified human interleukin-2. This recombinant form differs from native interleukin-2 in the following ways: a) Proleukin is not glycosylated because it is derived from *E. coli*. b) The molecule has no N-terminal alanine, the codon for this amino acid was deleted during the genetic engineering procedure. c) The molecule has serine substituted for cysteine at amino acid position 125, this was accomplished by site specific manipulation during the genetic engineering procedure, and d) the aggregation state of Proleukin is likely to be different from that of native interleukin-2.

Biological activities tested *in vitro* for the native non-recombinant molecule have been reproduced with Proleukin.[1,2]

Proleukin for Injection is supplied as a sterile, white to off-white, lyophilized cake in single-use vials intended for intravenous (IV) administration. When reconstituted with 1.2 mL Sterile Water for Injection, USP each mL contains 18 million IU (1.1 mg) Proleukin, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2 to 7.8). The manufacturing process for Proleukin involves fermentation in a defined medium containing tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. Proleukin contains no preservatives in the final product.

Proleukin biological potency is determined by a lymphocyte proliferation bioassay and is expressed in International Units (IU) as established by the World Health Organization 1st International Standard for interleukin-2 (human). The relationship between potency and protein mass is as follows:

18 million (18×10^6) IU Proleukin® = 1.1 mg protein

CLINICAL PHARMACOLOGY

Proleukin® has been shown to possess the biological activity of human native interleukin-2.[1,2] *In vitro* studies performed on human cell lines demonstrate the immunoregulatory properties of Proleukin, including: a) enhancement of lymphocyte mitogenesis and stimulation of long-term growth of human interleukin-2 dependent cell lines; b) enhancement of lymphocyte cytotoxicity; c) induction of killer cell [lymphokine-activated (LAK) and natural (NK)] activity; and d) induction of interferon-gamma production.

The *in vivo* administration of Proleukin in select murine tumor models and in the clinic produces multiple immunological effects in a dose dependent manner. These effects include activation of cellular immunity with profound lymphocytosis, eosinophilia, and thrombocytopenia; and the production of cytokines including tumor necrosis factor, IL-1 and gamma interferon.[3] *In vivo* experiments in murine tumor models have shown inhibition of tumor growth.[4] The exact mechanism by which Proleukin mediates its antitumor activity in animals and humans is unknown.

Pharmacokinetics: Proleukin exists as biologically active, non-covalently bound microaggregates with an average size of 27 recombinant interleukin-2 molecules. The solubilizing agent, sodium dodecyl sulfate, may have an effect on the kinetic properties of this product. The pharmacokinetic profile of Proleukin is characterized by high plasma concentrations following a short IV infusion, rapid distribution to extravascular, extracellular space and elimination from the body by metabolism in the kidneys with little or no bioactive protein excreted in the urine.

Studies of IV Proleukin in sheep and humans indicate that approximately 30% of the administered dose initially distributes to the plasma.

This is consistent with studies in rats that demonstrate a rapid (< 1 minute) and preferential uptake of approximately 70% of an administered dose into the liver, kidney and lung.

The serum half-life (T 1/2) curves of Proleukin remaining in the plasma are derived from studies done in 52 cancer patients following a 5 minute IV infusion.[5] These patients were shown to have a distribution and elimination T 1/2 of 13 and 85 minutes, respectively.

The relatively rapid clearance rate of Proleukin has led to dosage schedules characterized by frequent, short infusions. Observed serum levels are proportional to the dose of Proleukin.

Following the initial rapid organ distribution described above, the primary route of clearance of circulating Proleukin is the kidney. In humans and animals, Proleukin is cleared from the circulation by both glomerular filtration and peritubular extraction in the kidney.[6-9] This dual mechanism for delivery of Proleukin to the proximal tubule may account for the preservation of clearance in patients with rising serum creatinine values. Greater than 80% of the amount of Proleukin distributed to plasma, cleared from the circulation and presented to the kidney is metabolized to amino acids in the cells lining the proximal convoluted tubules. In humans, the mean clearance rate in cancer patients is 268 mL/min.[5]

Immunogenicity: Fifty-eight of 76 renal cancer patients (76%) treated with the every 8 hour Proleukin regimen developed low titers of non-neutralizing anti-interleukin-2 antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (< 1%) patients treated with IV Proleukin using a wide variety of schedules and doses. The clinical significance of anti-interleukin-2 antibodies is unknown.

Clinical Experience: Two hundred and fifty-five patients with metastatic renal cell cancer were treated with single agent Proleukin. Treatment was given by the every 8 hour regimen in 7 clinical studies conducted at 21 institutions. To be eligible for study, patients were required to have bidimensionally measurable disease, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1 (see Table I), and normal organ function, including normal cardiac stress test and pulmonary function tests. Patients with brain metastases, active infections, organ allografts and diseases requiring steroid treatment were excluded. In addition, it was noted that 218 of the 255 (85%) patients had undergone nephrectomy prior to treatment with Proleukin.

Proleukin was given by 15 minute IV infusion every 8 hours for up to 5 days (maximum of 14 doses). No treatment was given on days 6 to 14 and then dosing was repeated for up to 5 days on days 15 to 19 (maximum of 14 doses). These 2 cycles constituted 1 course of therapy. All patients were treated with 28 doses or until dose-limiting toxicity occurred requiring ICU-level support. Patients received a median of 20 of 28 scheduled doses of Proleukin. Doses were held for specific toxicities (See "**DOSAGE AND ADMINISTRATION**" Section "**Dose Modification**" Subsection). A variety of serious adverse events were encountered including: hypotension, oliguria/anuria;

mental status changes including coma, pulmonary congestion and dyspnea, GI bleeding, respiratory failure leading to intubation, ventricular arrhythmias, myocardial ischemia and/or infarction, ileus or intestinal perforation, renal failure requiring dialysis, gangrene, seizures, sepsis and death (See "**ADVERSE REACTIONS**" Section)

Due to the toxicities encountered during the clinical trials, investigators used the following concomitant medications: Acetaminophen and indomethacin were started immediately prior to Proleukin to reduce fever. Renal function was particularly monitored because indomethacin may cause synergistic nephrotoxicity. Meperidine was added to control the rigors associated with fever. Ranitidine or cimetidine were given for prophylaxis of gastrointestinal irritation and bleeding. Antiemetics and antidiarrheals were used as needed to treat other gastrointestinal side effects. These medications were discontinued 12 hours after the last dose of Proleukin. Hydroxyzine or diphenhydramine were used to control symptoms from pruritic rashes and continued until resolution of pruritis. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the package insert for the respective product.**

For the 255 patients in the Proleukin database, objective response was seen in 15% or 37 patients with nine (4%) complete and 28 (11%) partial responders. The 95% confidence interval for response was 11 to 20%. Onset of tumor regression has been observed as early as 4 weeks after completion of the first course of treatment and tumor regression may continue for up to 12 months after the start of treatment. Durable responses were achieved with a median duration of objective (partial or complete) response by Kaplan-Meier projection of 23.2 months (1 to 50 months). The median duration of objective partial response was 18.8 months. The proportion of responding patients who will have response durations of 12 months or greater is projected to be 85% for all responders and 79% for patients with partial responses (Kaplan-Meier).

Complete Responders	Partial Responders	Response Rate	Onset of Response	Median Duration of Response
9 (4%)	28 (11%)	15%	1 to 12 mos.	23.2 months (range 1-50)

Response was observed in both lung and non-lung sites (e.g. liver, lymph node, renal bed recurrences, soft tissue). Patients with individual bulky lesions ($> 5 \times 5$ cm) as well as large cumulative tumor burden (> 25 cm^2 tumor area) achieved durable responses.

An analysis of prognostic factors showed that performance status as defined by the ECOG (see Table I) was a significant predictor of response. PS 0 patients had an 18% overall rate of objective response, which included all 9 complete response patients and 21 of 28 partial response patients. PS 1 patients had a lower rate of response (9%), all of which were partial responses. In this group it was notable that 6 of the 7 responders had resolution of tumor related symptoms and improved performance status to PS 0. All seven patients were fully functional and 4 of the 7 returned to work, suggesting that responses among the PS 1 patients were clinically meaningful as well (see Table II).

In addition, the frequency of toxicity was related to the performance status. As a group, PS 0 patients, when compared with PS 1 patients, had lower rates of adverse events with fewer on-study deaths (4% vs. 6%), less frequent intubations (8% vs. 25%), gangrene (0% vs. 6%), coma (1% vs. 6%), GI bleeding (4% vs. 8%), and sepsis (6% vs. 18%). These differences in toxicity are reflected in the shorter mean time to hospital discharge for PS 0 patients (2 vs. 3 days) as well as the smaller percentage of PS 0 patients experiencing a delayed (> 7 days) discharge from the hospital (8% vs. 19%).

TABLE I
PERFORMANCE STATUS SCALE

Performance Status Equivalent		Performance Status Definitions
ECOG*	Karnofsky	
0	100	Asymptomatic
1	80-90	Symptomatic, fully ambulatory
2	60-70	Symptomatic, in bed less than 50% of day
3	40-50	Symptomatic, in bed more than 50% of day
4	20-30	Bedridden

Zubrod, CG, et al. J Chron Dis 11 7-33, 1960

TABLE II
PROLEUKIN RESPONSE ANALYZED BY ECOG* PERFORMANCE STATUS (PS)

Pre-Treatment ECOG PS	No. of Patients Treated (n = 255)	Response CR	Response PR	% of Patients Responding	On-Study Death Rate
0	166	9	21	18%	4%
1	80	0	7	9%	6%
≥ 2	9	0	0	0%	0%

*Eastern Cooperative Oncology Group

INDICATIONS AND USAGE

Proleukin (aldesleukin) is indicated for the treatment of adults (≥ 18 years of age) with metastatic renal cell carcinoma.

Careful patient selection is mandatory prior to the administration of Proleukin. See "**CONTRAINDICATIONS**", "**WARNINGS**" and "**PRECAUTIONS**" Sections regarding patient screening, including recommended cardiac and pulmonary function tests and laboratory tests.

*Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS 0) at treatment initiation respond better to Proleukin, with a higher response rate and lower toxicity (See "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection). Therefore, selection of patients for treatment should include assessment of performance status, as described in Table I.*

Experience in patients with PS > 1 is extremely limited.

CONTRAINDICATIONS

Proleukin (aldesleukin) is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the Proleukin formulation.

Patients with an abnormal thallium stress test or pulmonary function tests are excluded from treatment with Proleukin. Patients with organ allografts should be excluded as well. In addition, retreatment with Proleukin is contraindicated in patients who experienced the following *toxicities while receiving an earlier course of therapy:*

- Sustained ventricular tachycardia (≥ 5 beats)
- Cardiac rhythm disturbances not controlled or unresponsive to management
- Recurrent chest pain with ECG changes, consistent with angina or myocardial infarction
- Intubation required > 72 hours
- Pericardial tamponade
- Renal dysfunction requiring dialysis > 72 hours
- Coma or toxic psychosis lasting > 48 hours
- Repetitive or difficult to control seizures
- Bowel ischemia/perforation
- GI bleeding requiring surgery

WARNINGS

See boxed "**WARNINGS**"

Proleukin (aldesleukin) administration has been associated with capillary leak syndrome (CLS) which results from extravasation of plasma proteins and fluid into the extravascular space and loss of vascular tone. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. The CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, and mental status changes.

Because of the severe adverse events which generally accompany Proleukin therapy at the recommended dosages, thorough clinical evaluation should be performed to exclude from treatment patients with significant cardiac, pulmonary, renal, hepatic or CNS impairment.

Should adverse events occur, which require dose modification, dosage should be withheld rather than reduced. (See "**DOSAGE AND ADMINISTRATION**" Section, "**Dose Modification**" Subsection).

Proleukin may exacerbate disease symptoms in patients with clinically unrecognized or untreated CNS metastases. All patients should have thorough evaluation and treatment of CNS metastases prior to receiving Proleukin therapy. They should be neurologically stable with a negative CT scan. In addition, extreme caution should be exercised in treating patients with a history of seizure disorder because Proleukin may cause seizures.

Intensive Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis, in treated patients. Consequently, pre-existing bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Additionally, all patients with indwelling central lines should receive antibiotic prophylaxis effective against *S aureus*.[10-12] Antibiotic prophylaxis which has been associated with a reduced incidence of staphylococcal infections in Proleukin studies includes the use of: oxacillin, nafcillin, ciprofloxacin, or vancomycin. Disseminated infections acquired in the course of Proleukin treatment are a major contributor to treatment morbidity and use of antibiotic prophylaxis and aggressive treatment of suspected and documented infections may reduce the morbidity of Proleukin treatment. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the package insert for the respective product.**

PRECAUTIONS

General: Patients should have normal cardiac, pulmonary, hepatic and CNS function at the start of therapy. Patients who have had a nephrectomy are still eligible for treatment if they have serum creatinine levels ≤ 1.5 mg/dL.

Adverse events are frequent, often serious, and sometimes fatal.

Capillary leak syndrome (CLS) begins immediately after Proleukin treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone. In most patients, this results in a concomitant drop in mean arterial blood pressure within 2 to 12 hours after the start of treatment. With continued therapy, clinically significant hypotension (defined as systolic blood pressure below 90 mm Hg or a 20 mm Hg drop from baseline systolic pressure) and hypoperfusion will occur. In addition, extravasation of protein and fluids into the extravascular space will lead to edema formation and creation of effusions.

Medical management of CLS begins with careful monitoring of the patient's fluid and organ perfusion status. This is achieved by frequent determination of blood pressure and pulse, and by monitoring organ function, which includes assessment of mental status and urine output. Hypovolemia is assessed by catheterization and central pressure monitoring.

Flexibility in fluid and pressor management is essential for maintaining organ perfusion and blood pressure. Consequently, extreme caution should be used in treating patients with fixed requirements for large volumes of fluid (e.g. patients with hypercalcemia).

Patients with hypovolemia are managed by administering IV fluids, either colloids or crystalloids. IV fluids are usually given when the central venous pressure (CVP) is below 3 to 4 mm H_2O. Correction of hypovolemia may require large volumes of IV fluids but caution is required because unrestrained fluid administration may exacerbate problems associated with edema formation or effusions.

With extravascular fluid accumulation, edema is common and some patients may develop ascites or pleural effusions. Management of these events depends on a careful balancing of the effects of fluid shifts so that neither the consequences of hypovolemia (e.g. impaired organ perfusion) nor the consequences of fluid accumulations (e.g. pulmonary edema) exceeds the patient's tolerance.

Clinical experience has shown that early administration of dopamine (1 to 5 μg/kg/min) to patients manifesting capillary leak syndrome, before the onset of hypotension, can help to maintain organ perfusion particularly to the kidney and thus preserve urine output. Weight and urine output should be carefully monitored. If organ perfusion and blood pressure are not sustained by dopamine therapy, clinical investigators have increased the dose of dopamine to 6 to 10 μg/kg/min or have added phenylephrine hydrochloride (1 to 5 μg/kg/min) to low dose dopamine. (See "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection). Prolonged use of pressors, either in combination or as individual agents, at relatively high doses, may be associated with cardiac rhythm disturbances. **NOTE: Prior to the use of any product mentioned in this paragraph, the physician should refer to the package insert for the respective product.**

Failure to maintain organ perfusion, demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias, should lead to holding the subsequent doses until recovery of organ perfusion and a return of systolic blood pressure above 90 mm Hg are observed. (See "**DOSAGE AND ADMINISTRATION**" Section, "**Dose Modification**" Subsection).

Recovery from CLS begins soon after cessation of Proleukin therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and resorption of extravasated fluid and protein begins. If there has been excessive weight gain or edema formation, particularly if associated with shortness of breath from pulmonary congestion, use of diuretics, once blood pressure has normalized, has been shown to hasten recovery.

Oxygen is given to the patient if pulmonary function monitoring confirms that P_aO_2 is decreased.

Proleukin administration may cause anemia and/or thrombocytopenia. Packed red blood cell transfusions have been given both for relief of anemia and to insure maximal oxygen carrying capacity. Platelet transfusions have been given to resolve absolute thrombocytopenia and to reduce the risk of GI bleeding. In addition, leukopenia and neutropenia are observed.

Proleukin administration results in fever, chills, rigors, pruritus and gastrointestinal side effects in most patients treated at recommended doses. These side effects have been aggressively managed as described in the "**CLINICAL PHARMACOLOGY**" Section, "**Clinical Experience**" Subsection.

Renal and hepatic function is impaired during Proleukin treatment. Use of concomitant medications known to be nephrotoxic or hepatotoxic may further increase toxicity to the kidney or liver. In addition, reduced kidney and liver function secondary to Proleukin treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.

Patients may experience mental status changes including irritability, confusion, or depression while receiving Proleukin. These mental status changes may be indicators of bacteremia or early bacterial sepsis. Mental status changes due solely to Proleukin are generally reversible when drug administration is discontinued. However, alterations in mental status may progress for several days before recovery begins.

Impairment of thyroid function has been reported following Proleukin treatment. A small number of treated patients went on to require thyroid replacement therapy. This impairment of thyroid function may be a manifestation of autoimmunity; consequently, extra caution should be exercised when treating patients with known autoimmune disease.

Proleukin (aldesleukin) enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

Laboratory Tests: The following clinical evaluations are recommended for all patients, prior to beginning treatment and then daily during drug administration:

- Standard hematologic tests — including CBC, differential and platelet counts
- Blood chemistries — including electrolytes, renal and hepatic function tests
- Chest x-rays

All patients should have baseline pulmonary function tests with arterial blood gases. Adequate pulmonary function should be documented (FEV_1 >2 liters or ≥ 75% of predicted for height and age) prior to initiating therapy. All patients should be screened with a stress thallium study. Normal ejection fraction and unimpaired wall motion should be documented. If a thallium stress test suggests minor wall motion abnormalities of questionable significance, a stress echocardiogram to document normal wall motion may be useful to exclude significant coronary artery disease.

Daily monitoring during therapy with Proleukin should include vital signs (temperature, pulse, blood pressure and respiration rate) and weight. In a patient with a decreased blood pressure, especially less than 90 mm Hg, constant cardiac monitoring for rhythm should be conducted. If an abnormal complex or rhythm is seen, an ECG should be performed. Vital signs in these hypotensive patients should be taken hourly and central venous pressure (CVP) checked.

During treatment, pulmonary function should be monitored on a regular basis by clinical examination, assessment of vital signs and pulse oximetry. Patients with dyspnea or clinical signs of respiratory impairment (tachypnea or rales) should be further assessed with arterial blood gas determination. These tests are to be repeated as often as clinically indicated.

Cardiac function is assessed daily by clinical examination and assessment of vital signs. Patients with signs or symptoms of chest pain, murmurs, gallops, irregular rhythm or palpitations should be further assessed with an ECG examination and CPK evaluation. If there is evidence of cardiac ischemia or congestive heart failure, a repeat thallium study should be done.

Drug Interactions: *Proleukin may affect central nervous function. Therefore, interactions could occur following concomitant administration of psychotropic drugs (e.g., narcotics, analgesics, antiemetics, sedatives, tranquilizers).*

Concurrent administration of drugs possessing nephrotoxic (e.g. aminoglycosides, indomethacin), myelotoxic (e.g. cytotoxic chemotherapy), cardiotoxic (e.g. doxorubicin) or hepatotoxic (e.g. methotrexate, asparaginase) effects with Proleukin may increase toxicity in these organ systems. The safety and efficacy of Proleukin in combination with chemotherapies has not been established.

Although glucocorticoids have been shown to reduce Proleukin-induced side effects including fever, renal insufficiency, hyperbilirubinemia, confusion and dyspnea,[13] concomitant administration of these agents with Proleukin may reduce the antitumor effectiveness of Proleukin *and thus should be avoided.*

Beta-blockers and other antihypertensives may potentiate the hypotension seen with Proleukin (aldesleukin).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no studies conducted assessing the carcinogenic or mutagenic *potential of Proleukin (aldesleukin).*

There have been no studies conducted assessing the effect of Proleukin on fertility. It is recommended that this drug not be administered to fertile persons of either sex not practicing effective contraception.

Pregnancy: *Pregnancy Category C. Animal reproduction studies have not been conducted with Proleukin. It is also not known whether* Proleukin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In view of the known adverse effects of Proleukin, it should only be given to a pregnant woman with extreme caution, weighing the potential benefit with the risks associated with therapy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Proleukin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children under 18 years of age have not been established.

ADVERSE REACTIONS

The rate of drug related deaths in the 255 metastatic renal cell carcinoma patients on study who received single-agent Proleukin was 4% (11/255).

Frequency and severity of adverse reactions to Proleukin have generally been shown to be dose-related and schedule-dependent. Most adverse reactions are self-limiting and are usually, but not invariably, reversible within 2 or 3 days of discontinuation of therapy.

Examples of adverse reactions with permanent sequelae include: myocardial infarction, bowel perforation/infarction, and gangrene.

The most frequently reported serious adverse reactions include hypotension, renal dysfunction with oliguria/anuria, dyspnea or pulmonary congestion, and mental status changes (i.e., lethargy, somnolence, confusion and agitation). Other serious toxicities have included: myocardial ischemia, myocarditis, gangrene, respiratory failure leading to intubation, GI bleeding *requiring surgery, intestinal perforation/ileus,* coma, seizure, sepsis and renal impairment requiring dialysis. The incidence of these events has been higher in PS 1 patients than in PS 0 patients (See **"CLINICAL PHARMACOLOGY"** Section, **"Clinical Experience"** Subsection).

The following data on adverse reactions are based on 373 patients (255 with renal cell cancer and 118 with other tumors) treated with the recommended every 8 hour 15-minute infusion dosing regimen. These patients had metastatic or recurrent carcinoma and were enrolled in investigational trials in the United States.

Organ systems in which reactions occurred in a significant number of the patients treated are found in the following table:

TABLE III
Incidence of Adverse Events

Events by Body System	% of Patients	Events by Body System	% of Patients
Cardiovascular		Gastrointestinal	
Hypotension	85	Nausea and Vomiting	87
(requiring pressors)	71	Diarrhea	76
Sinus Tachycardia	70	Stomatitis	32
Arrhythmias	22	Anorexia	27
Atrial	8	GI Bleeding	13
Supraventricular	5	(requiring surgery)	2
Ventricular	3	Dyspepsia	7
Junctional	1	Constipation	5
Bradycardia	7	Intestinal Perforation/Ileus	2
Premature Ventricular Contractions	5	Pancreatitis	<1
Premature Atrial Contractions	4	Neurologic	
Myocardial Ischemia	3	Mental Status Changes	73
Myocardial Infarction	2	Dizziness	17
Cardiac Arrest	2	Sensory Dysfunction	10
Congestive Heart Failure	1	Special Sensory Disorders	
Myocarditis	1	(vision, speech, taste)	7
Stroke	1	Syncope	3
Gangrene	1	Motor Dysfunction	2
Pericardial Effusion	1	Coma	1
Endocarditis	1	Seizure (grand mal)	1
Thrombosis	1		

ABLE III — Continued
Incidence of Adverse Events

Events by Body System	% of Patients
Pulmonary	
Pulmonary Congestion	54
Dyspnea	52
Pulmonary Edema	10
Respiratory Failure (leading to intubation)	9
Tachypnea	8
Pleural Effusion	7
Wheezing	6
Apnea	1
Pneumothorax	1
Hemoptysis	1
Hepatic	
Elevated Bilirubin	64
Elevated Transaminase	56
Elevated Alkaline Phosphates	56
Jaundice	11
Ascites	4
Hepatomegaly	1
Hematologic	
Anemia	77
Thrombocytopenia	64
Leukopenia	34
Coagulation Disorders	10
Leukocytosis	9
Eosinophilia	6
Abnormal Laboratory Findings	
Hypomagnesemia	16
Acidosis	16
Hypocalcemia	15
Hypophosphatemia	11
Hypokalemia	9
Hyperuricemia	9
Hypoalbuminemia	8
Hypoproteinemia	7
Hyponatremia	4
Hyperkalemia	4
Alkalosis	4
Hypoglycemia	2
Hyperglycemia	2
Hypocholesterolemia	1
Hypercalcemia	1
Hypernatremia	1
Hyperphosphatemia	1

Events by Body System	% of Patients
Renal	
Oliguria/Anuria	76
BUN Elevation	63
Serum Creatinine Elevation	61
Proteinuria	12
Hematuria	9
Dysuria	3
Renal Impairment Requiring Dialysis	2
Urinary Retention	1
Urinary Frequency	1
Dermatologic	
Pruritis	48
Erythema	41
Rash	26
Dry Skin	15
Exfoliative Dermatitis	14
Purpura/Petechiae	4
Urticaria	2
Alopecia	1
Musculoskeletal	
Arthralgia	6
Myalgia	6
Arthritis	1
Muscle Spasm	1
Endocrine	
Hypothyroidism	<1
General	
Fever and/or Chills	89
Pain (all sites)	54
Abdominal	15
Chest	12
Back	9
Fatigue/Weakness/Malaise	53
Edema	47
Infection including urinary tract, injection site, catheter tip, phlebitis, sepsis)	23
Weight Gain (≥ 10%)	23
Headache	12
Weight Loss (≥ 10%)	5
Conjunctivitis	4
Injection Site Reactions	3
Allergic Reactions (non-anaphylactic)	1

Other serious adverse events were derived from trials involving more than 1,800 patients treated with Proleukin-based regimens using a variety of doses and schedules. These events each occurred with a frequency of < 1% and included: liver or renal failure resulting in death, duodenal ulceration, fatal intestinal perforation, bowel necrosis, fatal cardiac arrest, myocarditis, and supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; fatal malignant hyperthermia; pulmonary edema resulting in death; respiratory arrest, fatal respiratory failure; fatal stroke; transient ischemic attack; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula; fatal pulmonary emboli; severe depression leading to suicide.

OVERDOSAGE

Side effects following the use of Proleukin are dose-related. Administration of more than the recommended dose has been associated with a more rapid onset of expected dose limiting toxicities. Adverse reactions generally will reverse when the drug is stopped, particularly because its serum half-life is short (See "**CLINICAL PHARMACOLOGY**" Section, "**Pharmacokinetics**" Subsection). Any continuing symptoms should be treated supportively. Life threatening toxicities have been ameliorated by the intravenous administration of dexamethasone [1] which may result in loss of therapeutic effect from Proleukin. **NOTE: Prior to the use of dexamethasone, the physician should refer to the package insert for this product.**

DOSAGE AND ADMINISTRATION

Proleukin (aldesleukin for injection) should be administered by a 15-minute IV infusion every 8 hours. Before initiating treatment, carefully review the "**INDICATIONS**", "**CONTRAINDICATIONS**", "**WARNINGS**", "**PRECAUTIONS**", and "**ADVERSE REACTIONS**" Sections, particularly regarding patient selection, possible serious adverse events, patient monitoring and withholding dosage.

The following schedule has been used to treat adult patients with metastatic renal cell carcinoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV infusion for a total of 14 doses.
Following 9 days of rest, the schedule is repeated for another 14 doses, for a maximum of 28 doses per course.

During clinical trials, doses were frequently held for toxicity (See "**Dose Modification**" Subsection). Patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy.

Retreatment: Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment may be given to patients only if there is some tumor shrinkage following the last course and retreatment is not contraindicated (See "**CONTRAINDICATION**" Section). Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge. Tumors have continued to regress up to 12 months following the initiation of Proleukin therapy.

Dose Modification: Dose modification for toxicity should be accomplished by holding or interrupting a dose rather than reducing the dose to be given. Decisions to stop, hold, or restart Proleukin therapy must be made after a global assessment of the patient. With this in mind, the following guidelines should be used:

Treatment with Proleukin (aldesleukin) should be permanently discontinued for:

Organ System	Permanently discontinue treatment for the following toxicities
Cardiovascular	Sustained ventricular tachycardia (≥ 5 beats)
	Cardiac rhythm disturbances not controlled or unresponsive to management
	Recurrent chest pain with ECG changes, documented angina or myocardial infarction
	Pericardial tamponade
Pulmonary	Intubation required > 72 hours
Renal	Renal dysfunction requiring dialysis > 72 hours
Central Nervous System	Coma or toxic psychosis lasting > 48 hours
	Repetitive or difficult to control seizures
Gastrointestinal	Bowel ischemia/perforation/GI bleeding requiring surgery

Doses should be held and restarted according to the following

Organ System	Hold dose for	Subsequent doses may be given if
Cardiovascular	Atrial fibrillation, supraventricular tachycardia, or bradycardia that requires treatment or is recurrent or persistent	Patient is asymptomatic with full recovery to normal sinus rhythm.
	Systolic bp <90 mm Hg with increasing requirements for pressors	Systolic bp ≥ 90 mm Hg and stable or improving requirements for pressors
	Any ECG change consistent with MI or ischemia with or without chest pain; suspicion of cardiac ischemia	Patient is asymptomatic, MI has been ruled out, clinical suspicion of angina is low
Pulmonary	O_2 saturation $<94\%$ on room air or $<90\%$ with 2 liters O_2 by nasal prongs	O_2 saturation $\geq 94\%$ on room air or $\geq 90\%$ with 2 liters O_2 by nasal prongs
Central Nervous System	Mental status changes, including moderate confusion or agitation	Mental status changes completely resolved
Systemic	Sepsis syndrome, patient is clinically unstable	Sepsis syndrome has resolved, patient is clinically stable, infection is under treatment
Renal	Serum creatinine ≥ 4.5 mg/dl or a serum creatinine of 4 mg/dl in the presence of severe volume overload, acidosis, or hyperkalemia	Serum creatinine <4 mg/dl and fluid and electrolyte status is stable
	Persistent oliguria, urine output of ≤ 10 mL/hour for 16 to 24 hours with rising serum creatinine	Urine output >10 mL/hour with a decrease of serum creatinine ≥ 1.5 mg/dl or normalization of serum creatinine
Hepatic	Signs of hepatic failure including encephalopathy, increasing ascites, liver pain, hypoglycemia	All signs of hepatic failure have resolved*
Gastrointestinal	Stool guaiac repeatedly >3-4+	Stool guaiac negative
Skin	Bullous dermatitis or marked worsening of pre-existing skin condition (avoid topical steroid therapy)	Resolution of all signs of bullous dermatitis

*Discontinue all further treatment for that course. Consider starting a new course of treatment at least 7 weeks after cessation of adverse event and hospital discharge.

Reconstitution and Dilution Directions:
Reconstitution and dilution procedures other than those recommended may alter the delivery and/or pharmacology of Proleukin and thus should be avoided.

1 Proleukin is a sterile, white to off-white, preservative-free, lyophilized powder suitable for IV infusion upon reconstitution and dilution. **EACH VIAL CONTAINS 22 MILLION IU (1.3 MG) OF PROLEUKIN AND SHOULD BE RECONSTITUTED ASEPTICALLY WITH 1.2 ML OF STERILE WATER FOR INJECTION, USP. WHEN RECONSTITUTED AS DIRECTED, EACH ML CONTAINS 18 MILLION IU (1.1 MG) OF PROLEUKIN.** The resulting solution should be a clear, colorless to slightly yellow liquid. The vial is for single-use only and any unused portion should be discarded.

2 During reconstitution, the Sterile Water for Injection, USP should be directed at the side of the vial and the contents gently swirled to avoid excess foaming. **DO NOT SHAKE.**

3 The dose of Proleukin, reconstituted in Sterile Water for Injection, USP (without preservative) should be diluted aseptically in 50 mL of 5% Dextrose Injection, USP and infused over a 15-minute period. Although glass bottles and plastic (polyvinyl chloride) bags have been used in clinical trials with comparable results, it is recommended that plastic bags be used as the dilution container since experimental studies suggest that use of plastic containers results in more consistent drug delivery. In-line filters should not be used when administering Proleukin.

4 Before and after reconstitution and dilution, store in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Administer Proleukin within 48 hours of reconstitution. The solution should be brought to room temperature prior to infusion in the patient.

5 Reconstitution or dilution with Bacteriostatic Water for Injection, USP, or 0.9% Sodium Chloride Injection, USP should be avoided because of increased aggregation. Animal studies have shown that dilution with albumin can alter the pharmacology of Proleukin. Proleukin for Injection should not be mixed with other drugs.

6 Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Proleukin (aldesleukin for injection) is supplied in packs of ten individually-boxed single-use vials. Each vial contains 22×10^6 IU of Proleukin. Discard unused portion.

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Store vials of lyophilized Proleukin for Injection in a refrigerator at 2° to 8°C (36° to 46°F).

Reconstituted or diluted Proleukin is stable for up to 48 hours at refrigerated and room temperatures, 2° to 25°C (36° to 77°F). However, since this product contains no preservative, the reconstituted and diluted solutions should be stored in the refrigerator.

Do not use beyond the expiration date printed on the vial. **Note:** This product contains no preservative.

CAUTION: Federal law (USA) prohibits dispensing without a prescription.

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